L10: Entry 5 of 6 File: DWPI May 1, 1998

DERWENT-ACC-NO: 1997-145355
DERWENT-WEEK: 200007

TITLE: Use of new and known 1-alkyl-1,4-di:hydro-4-oxo-N-substd naphthyridine-3-carboxamide derivs - for treating conditions modulated by phosphodiesterase IV or tumour necrosis factor

INVENTOR: BAXTER, A D; BEASLEY, S C ; BUCKLEY, G M ; DYKE, H J ; HAUGHAN, A F ; KENDALL, H J ; MANALLACK, D T ; MAXEY, R J ; MONTANA, J G ; RUNCIE, K A ; HAUGHAN, F A

PATENT-ASSIGNEE:

ASSIGNEE	CODE
CHIROSCIENCE LTD	CHIRN
DARWIN DISCOVERY LTD	DARWN

PRIORITY-DATA: 1996GB-0011898 (June 7, 1996), 1995GB-0015812 (August 2, 1995), 1995GB-0023679 (November 20, 1995), 1996GB-0005865 (March 20, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
MX 9800921 A1	May 1, 1998	N/A	000	A61K031/435
WO 9704775 A1	February 13, 1997	E	033	A61K031/435
AU 9666266 A	February 26, 1997	N/A	000	N/A
ZA 9606600 A	October 29, 1997	N/A	031	A61K000/00
EP 841927 A1	May 20, 1998	E	000	N/A
US 5753666 A	May 19, 1998	N/A	000	A01N043/54
AU 695132 B	August 6, 1998	N/A	000	N/A
JP 11510156 W	September 7, 1999	N/A	037	A61K031/44

DESIGNATED-STATES: AL AM AU AZ BB BG BR BY CA CN CU CZ EE GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LV MD MG MK MN MW MX NO NZ PL RO RU SD SG SI SK TJ TM TR TT UA UG UZ VN AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

CITED-DOCUMENTS:6.Jnl.Ref; JP 2124871 ; US 3524858 ; US 4621088 ; US 4786644

APPLICATION-DATA:

Storke
HIV
Other Viral - influenza
therapy

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
MX 9800921A1	February 2, 1998	1998MX-0000921	N/A
WO 9704775A1	July 31, 1996	1996WO-GB01866	N/A
AU 9666266A	July 31, 1996	1996AU-0066266	N/A
AU 9666266A		WO 9704775	Based on
ZA 9606600A	August 2, 1996	1996ZA-0006600	N/A
EP 841927A1	July 31, 1996	1996EP-0925909	N/A
EP 841927A1	July 31, 1996	1996WO-GB01866	N/A
EP 841927A1		WO 9704775	Based on
US 5753666A	August 2, 1996	1996US-0691339	N/A
AU 695132B	July 31, 1996	1996AU-0066266	N/A
AU 695132B		AU 9666266	Previous Publ.
AU 695132B		WO 9704775	Based on
JP 11510156W	July 31, 1996	1996WO-GB01866	N/A
JP 11510156W	July 31, 1996	1997JP-0507375	N/A
JP 11510156W		WO 9704775	Based on

INT-CL (IPC): A01N 43/54; A61K 0/00; A61K 31/00; A61K 31/435; A61K 31/44; A61K 31/47; A61K 31/505; C07D 471/00; C07D 471/04

RELATED-ACC-NO: 1997-153912

ABSTRACTED-PUB-NO: US 5753666A
BASIC-ABSTRACT:

The use of 1-alkyl-4-(thi)oxo-naphthyridine-3-carboxamide derivs. and -pyrido(2,3-d)pyrimidine analogues of formula (I), their salts, solvates and/or hydrates in the mfr. of a medicament for treating disease states modulated by phosphodiesterase IV (PDE IV) or tumour necrosis factor (TNF) inhibition is new. R1 = 1-6C alkyl, 1-6C alkylcycloalkyl, 1-6C alkyl-heterocyclo, 1-6C alkylaryl or 1-6C alkylheteroaryl all opt. substd. by 1 or more T, 1-6C alkyl or SO2NR11R12; T = halo, 1-6C alkoxy, OH, CN, COOH (or its 1-6C alkyl ester or 1-6C alkylamide) or NR9R10; R3 = phenyl, pyridyl, thienyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl or 3-10C cycloalkyl all opt. fused to a carbocyclic or heterocyclic ring and both rings opt. substd. by T, 1-6C alkyl, 1-6C haloalkyl, SO2NR11R12, aryl, heteroaryl, cycloalkyl or heterocyclo; Y = O or S; X = CR5 or N; Q = CR7 or N; R4-R7 = H, T, or 1-6C alkyl (opt. substd. by T or SO2NR11R12); or two adjacent R4-R7 gps. complete a 5- or 6-membered ring opt. contg. 1 or 2 heteroatoms; R9, R10 = H, 1-6C alkyl, aryl, heteroaryl, COCF3, SO2CF3, cycloalkyl, 1-6C C alkylcarbonyl, aroyl, 1-6C alkoxycarbonyl, arylsulphonyl or 1-6C alkylsulphonyl; or NR9R10 = 5- or 6-membered ring e.g. pyrrolidino, piperidino, morpholino or piperazino; R11, R12 = H, 1-6C alkyl or cycloalkyl; n = 0-3; provided that (1) at least 1 of X and Q = N; and (2) when R3 = substd. cyclohexyl and n = 1, the substituent is not COOH or its ester. Also claimed are cpds. (I) provided that when R3 is attached to (CH2)n at an aromatic atom, n = 1-3.

USE - (I) are useful for treating disease states associated with proteins which mediate cellular activity. (I) are partic. useful for treating disease states associated with a function of PDE IV, eosinophil accumulation or function or TNF (esp. inflammatory or autoimmune disease) such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation or allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis, arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic eczema, atopic dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke, intermittent claudication, joint inflammation, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, Gram negative sepsis, toxic shock syndrome, cerebral malaria, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft vs. host reaction, allograft rejection, malaria, myalgia, HIV, AIDS, ARC, cachexia, pyresis, systemic lupus

erythematosus, multiple sclerosis, type 1 diabetes mellitus, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukaemia or tardive dyskinesia (all claimed).

(I) are also useful as gastro-protectants and agents for treating yeast or fungal infections (claimed) (e.g. fungal meningitis).

(I) can also be used to treat viruses sensitive to TNF inhibition e.g. HIV-1, -2 or -3, cytomegalovirus, influenza, adenovirus, Herpes viruses (e.g. Herpes zoster and Herpes simplex), feline immunodeficiency virus and other animal retroviruses such as equine infectious anaemia, caprine arthritis, visna virus, maedi virus and other lentiviruses.

The excluded cpds. are disclosed in US4621088.

Dose is 0.001-20 mg/kg/day. Admin. is oral, rectal, topical, parenteral or via the respiratory tract.
ABSTRACTED-PUB-NO:

WO 9704775A
EQUIVALENT-ABSTRACTS:

The use of 1-alkyl-4-(thi)oxo-naphthyridine-3-carboxamide derivs. and -pyrido(2,3-d)pyrimidine analogues of formula (I), their salts, solvates and/or hydrates in the mfr. of a medicament for treating disease states modulated by phosphodiesterase IV (PDE IV) or tumour necrosis factor (TNF) inhibition is new. R1 = 1-6C alkyl, 1-6C alkylcycloalkyl, 1-6C alkyl-heterocyclo, 1-6C alkylaryl or 1-6C alkylheteroaryl all opt. substd. by 1 or more T, 1-6C alkyl or SO2NR11R12; T = halo, 1-6C alkoxy, OH, CN, COOH (or its 1-6C alkyl ester or 1-6C alkylamide) or NR9R10; R3 = phenyl, pyridyl, thienyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl or 3-10C cycloalkyl all opt. fused to a carbocyclic or heterocyclic ring and both rings opt. substd. by T, 1-6C alkyl, 1-6C haloalkyl, SO2NR11R12, aryl, heteroaryl, cycloalkyl or heterocyclo; Y = O or S; X = CR5 or N; Q = CR7 or N; R4-R7 = H, T, or 1-6C alkyl (opt. substd. by T or SO2NR11R12); or two adjacent R4-R7 gps. complete a 5- or 6-membered ring opt. contg. 1 or 2 heteroatoms; R9, R10 = H, 1-6C alkyl, aryl, heteroaryl, COCF3, SO2CF3, cycloalkyl, 1-6C C alkylcarbonyl, aroyl, 1-6C alkoxycarbonyl, arylsulphonyl or 1-6C alkylsulphonyl; or NR9R10 = 5- or 6-membered ring e.g. pyrrolidino, piperidino, morpholino or piperazino; R11, R12 = H, 1-6C alkyl or cycloalkyl; n = 0-3; provided that (1) at least 1 of X and Q = N; and (2) when R3 = substd. cyclohexyl and n = 1, the substituent is not COOH or its ester. Also claimed are cpds. (I) provided that when R3 is attached to (CH2)n at an aromatic atom, n = 1-3.

USE - (I) are useful for treating disease states associated with proteins which mediate cellular activity. (I) are partic. useful for treating disease states associated with a function of PDE IV, eosinophil accumulation or function or TNF (esp. inflammatory or autoimmune disease) such as asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation or allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis, arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, atopic eczema, atopic dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke, intermittent claudication, joint inflammation, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, Gram negative sepsis, toxic shock syndrome, cerebral malaria, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft vs. host reaction, allograft rejection, malaria, myalgia, HIV, AIDS, ARC, cachexia, pyresis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukaemia or tardive dyskinesia (all claimed).

(I) are also useful as gastro-protectants and agents for treating yeast or fungal infections (claimed) (e.g. fungal meningitis).

(I) can also be used to treat viruses sensitive to TNF inhibition e.g. HIV-1, -2 or -3, cytomegalovirus, influenza, adenovirus, Herpes viruses (e.g. Herpes zoster and Herpes simplex), feline immunodeficiency virus and other animal retroviruses

such as equine infectious anaemia, caprine arthritis, visna virus, maedi virus and other lentiviruses.

The excluded cpds. are disclosed in US4621088.

Dose is 0.001-20 mg/kg/day. Admin. is oral, rectal, topical, parenteral or via the respiratory tract.

TITLE-TERMS: NEW ALKYL DI HYDRO OXO N SUBSTITUTE NAPHTHYRIDINE CARBOXAMIDE DERIVATIVE TREAT CONDITION MODULATE PHOSPHODIESTERASE IV TUMOUR NECROSIS FACTOR

ADDL-INDEXING-TERMS:
PYRROLO PYRIMIDINE

DERWENT-CLASS: B02 C02

CPI-CODES: B06-D02; C06-D02; B06-D06; C06-D06; B14-C03; C14-C03; B14-C09B; C14-C09B; B14-G02A; C14-G02A; B14-G02D; C14-G02D; B14-K01; C14-K01; B14-N17C; C14-N17C; B14-S04; C14-S04;

CHEMICAL-CODES:

Chemical Indexing M2 *01*
Fragmentation Code
C316 D010 D011 D012 D013 D014 D019 D020 D021 D022
D023 D024 D025 D040 D622 D770 D850 F010 F019 F020
F021 F029 G001 G002 G003 G010 G011 G012 G013 G019
G020 G021 G022 G029 G040 G050 G100 G111 G221 G299
G553 G563 H1 H103 H121 H122 H123 H141 H161 H181
H2 H201 H401 H402 H403 H404 H441 H442 H443 H444
H481 H482 H483 H484 H521 H522 H523 H541 H542 H543
H581 H582 H583 H584 H600 H608 H609 H621 H622 H623
H641 H642 H643 H681 H682 H683 H689 J0 J011 J012
J013 J014 J111 J112 J113 J131 J132 J133 J171 J172
J173 J211 J212 J231 J232 J271 J272 J273 J3 J311
J5 J521 J592 K353 K399 L142 L143 L145 L199 L910
L921 L922 L930 L941 L943 L999 M126 M136 M210 M211
M212 M213 M214 M215 M216 M220 M221 M222 M223 M224
M225 M226 M231 M232 M233 M240 M272 M273 M281 M282
M283 M311 M312 M313 M314 M315 M316 M320 M321 M322
M323 M331 M332 M333 M334 M340 M342 M343 M344 M353
M372 M373 M391 M392 M393 M412 M511 M512 M520 M521
M522 M530 M531 M532 M540 M541 M542 M630 M640 M650
M781 M800 M903 M904 P420 P421 P423 P433 P444 P446
P522 P616 P738 P816 P820 P922 P924 P943 V813
Ring Index
01605 01681 01683
Markush Compounds
199713-40701-U

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1997-046367

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=> d l8 ibib kwic 1-
YOU HAVE REQUESTED DATA FROM 16 ANSWERS - CONTINUE? Y/(N):y

L8   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:713343  CAPLUS
DOCUMENT NUMBER:          135:272894
TITLE:                    Preparation of .beta.-amino acid derivatives as
                          inhibitors of matrix metalloproteases and
                          TNF-.alpha.
INVENTOR(S):              Duan, Jingwu; King, Bryan W.; Decicco, Carl;
                          Maduskuie, Thomas P., Jr.; Voss, Matthew E.
PATENT ASSIGNEE(S):       Dupont Pharmaceuticals Company, USA
SOURCE:                   PCT Int. Appl., 483 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
     ---------------    ----  --------      ---------------   --------
     WO 2001070734       A2   20010927      WO 2001-US8336    20010315
         W:  AT, AU, BR, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, IL, IN,
             JP, KR, LT, LU, LV, NZ, PL, PT, RO, SE, SG, SI, SK, UA, VN, ZA,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, TR
PRIORITY APPLN. INFO.:                      US 2000-190183   P  20000317
                                            US 2000-235467   P  20000926
                                            US 2000-252062   P  20001120
OTHER SOURCE(S):          MARPAT 135:272894
TI   Preparation of .beta.-amino acid derivatives as inhibitors of
     matrix metalloproteases and TNF-.alpha.
AB   Novel .beta.-amino acid derivs. A-CR3R4aCR2R4NR1CO-X-Z-Ua-Xa-Ya-Za [A =
     CO2H, SH, CH2SH, S(O)Ra:NH (Ra = H, alkyl), P(O)(OH)2, etc.; X, Xa is
     absent or alkylene, alkenylene or alkynylene; Z is absent or substituted
     C3-13 carbocycle or 5-14 membered heterocycle; Ua is absent or O, NRa1
     [Ra1 = H, (un)substituted alkyl, alkenyl or alkynyl; Ra and Ra1 may form a
     ring], CO, CO2, O2C, CONRa1, S(O)p (p = 0-2), etc.; Ya is absent or O,
     NRa1, S(O)p or CO; Za is H, substituted C3-13 carbocycle or 5-14 membered
     heterocycle; R1 is H, alkyl, Ph, benzyl; R2 is Q (Q is H, substituted
     carbocycle or heterocycle), alkylene-Q, (CRaRa1)r1O(CRaRa1)r-Q (r, r1 =
     0-4), (CRaRa1)r1NRa(CRaRa1)r-Q, etc.; R3 = Q1 (Q1 is any group given for
     Q), alkylene-Q1, (CRaRa1)r1O(CRaRa1)r-Q1, (CRaRa1)r1NRa(CRaRa1)r-Q1, etc.;
     R4, R4a = H, substituted alkyl, alkenyl or alkynyl; alternatively R1 and
     R2, R1 and R3, R3 and R4a may form rings (with provisos)] or a
     stereoisomer or pharmaceutically acceptable salt were prepd. as
     metalloprotease and TNF-.alpha. inhibitors. Thus,
     N-hydroxy-1-[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]acetyl]-3-
     azetidinecarboxamide was prepd. by a multistep procedure involving
     reactions of Me 4-hydroxyphenylacetate, 2-methyl-4-quinolinylmethanol, and
     3-azetidinecarboxylic acid Me ester.
ST   amino acid beta prepn inhibitor metalloprotease TNF;
     heterocyclyl beta amino acid prepn inhibitor metalloprotease
     TNF; cycloalkyl beta amino acid prepn inhibitor
     metalloprotease TNF

L8   ANSWER 4 OF 16  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER:    2001394010  EMBASE
TITLE:               Involvement of protein kinase C in TNF.alpha. regulation of
                     trabecular matrix metalloproteinases and TIMPs.
AUTHOR:              Alexander J.P.; Acott T.S.
CORPORATE SOURCE:    T.S. Acott, Casey Eye Institute (CERES), Oregon Health
                     Sciences University, 3375 SW Terwilliger, Portland, OR
                     97201, United States. acott@ohsu.edu
SOURCE:              Investigative Ophthalmology and Visual Science, (2001)
                     42/12 (2831-2838).
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